Effectiveness of interventions that support penicillin allergy assessment and de-labelling of patients by non-allergy specialists: a systematic review protocol

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ABSTRACT

Objective: This review will systematically examine and synthesize the evidence evaluating the effectiveness and safety of interventions that enable non-allergy specialist health care workers to assess allergy risk in patients with reported penicillin allergies and subsequently remove erroneous allergy records.

Introduction: The potential benefits of removing erroneous penicillin allergy labels (de-labeling) are wide-ranging. Penicillin allergy assessment and de-labeling is an antibiotic stewardship priority. Delivery of such assessment and de-labeling by non-allergy specialists has been reported in several studies, but the effectiveness and safety have not been formally synthesized. This is a necessary step in the upscaling of penicillin allergy assessment services.

Inclusion criteria: This review will consider quantitative studies using appropriate designs. The studies will include adults and pediatric patients who have undergone penicillin allergy assessment and de-labeling by non-allergy specialists in any health care setting.

Methods: A range of databases will be searched to identify studies published in English, with no date limit. Unpublished studies and gray literature will also be searched. Title and abstract screening, and assessment of selected full texts against the inclusion criteria will be conducted by at least two independent reviewers. Identified studies will be assessed for methodological quality using standardized critical appraisal instruments. Data will be extracted and categorized using the EPOC taxonomy, and the effectiveness and safety of the intervention will be determined. Where possible, data will be pooled to facilitate meta-analysis. Data from heterogeneous studies will be reported narratively. The GRADE approach for grading the certainty of evidence will be followed.

Systematic review registration number: PROSPERO CRD42020219044

Keywords: antimicrobial stewardship; penicillin allergy assessment; penicillin allergy de-labeling

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Introduction

Approximately 6% of the general population in England[1] and 15% of hospital inpatients in England and elsewhere[2-4] have a record of penicillin allergy. Penicillin-based antibiotics are first-line treatment for many common infections; however, patients with penicillin allergy labels are usually treated with second-line antibiotics.[2] Second-line antibiotics are often more costly,[5-7] less effective in certain clinical circumstances,[1,8-10] and more toxic.[5] Moreover, they are often broader spectrum, which potentially increases a patient's risk of future infections with resistant bacteria.[5,11] Patients with

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penicillin allergy records are also associated with exposure to a greater number of antibiotics, increased length of hospital stay,[2,4] and higher hospital readmission rates,[12] all of which increase costs to health care systems.

However, more than 90% of individuals with a penicillin allergy label are not allergic to penicillin.[13] Assessing patients with penicillin allergy labels to identify those who are not allergic to penicillin, and then de-labeling them, has the potential to reduce second-line antibiotic use in favor of penicillin, thereby reducing the unintended consequences associated with second-line antibiotics.

Penicillin allergy assessment of patients with a reported penicillin allergy has traditionally been the domain of allergy experts. Allergy services in the UK and elsewhere are limited,[14] and many hospitals do not have direct access to such services. Furthermore, allergy services do not have capacity to assess and de-label the potentially large number of patients with reported allergies to penicillin. Traditional penicillin allergy testing requires skin testing prior to an oral challenge test, and this is still the main testing method in UK allergy centers. Therefore, penicillin allergy testing is resource-intensive. A less resource-intensive penicillin allergy de-labeling method uses a direct oral penicillin challenge in patients with a history consistent with low risk of future penicillin allergy, forgoing the need for skin testing.

Direct oral challenge testing makes allergy assessment possible outside allergy centers because it is quicker and less resource-intensive than the traditional skin test method. Non-allergy specialist researchers have explored penicillin allergy assessment and de-labeling of hospitalized patients[15,16] and found it to be safe and effective, resulting in increased use of penicillin antibiotics instead of second-line antibiotics with minimal evidence of side effects. Two systematic reviews have confirmed the safety and efficacy of direct oral challenge delivered by allergists and non-allergists as a method of de-labeling adults.[17,18] Other methods delivered by non-allergists, such as skin testing, have also been successfully delivered in the inpatient and outpatient settings.[19,20]

Leading allergists in the US have suggested that every physician needs to obtain an accurate drug intolerance history before avoiding a beta-lactam antibiotic (the broader group name that includes the penicillin antibiotic group) when it is the drug of choice. These allergists also postulate that addressing unconfirmed beta-lactam allergy on a large scale would lead to a dramatic reduction in the morbidity and mortality associated with unconfirmed beta-lactam allergy and reduce associated health care costs.[21] In September 2020, the American Academy of Allergy, Asthma and Immunology, together with the Infectious Diseases Society of America, wrote to the Centers for Medicare and Medicaid Services to urge US hospitals to include verification of penicillin allergy as part of its mandatory antibiotic stewardship programs.[22] More recently, the World Health Organization recommended antibiotic de-labeling as an effective antimicrobial stewardship strategy.[23] However, knowledge of the epidemiology of penicillin allergy labels and their association with antimicrobial resistance in low- and middle-income countries is sparse, as is the evidence for established antibiotic de-labeling pathways,[24] with the majority of studies occurring in high-income countries.

Penicillin allergy de-labeling is supported by health care workers and accepted by patients. Health care workers in a UK hospital reported frequently encountering patients with penicillin allergy records they believed to be erroneous, and recognized that incorrect penicillin allergy records were a problem.[25] An Australian study demonstrated patient acceptability for oral penicillin challenges to rule out penicillin allergy,[26] while a US study found that patients believed that penicillin allergy testing provided valuable medical information.[27]

Enabling the wider health care workforce to assess patients with penicillin allergy records and to de-label eligible patients is required to ensure penicillin allergy assessment and de-labeling at scale. Lin *et al.*[28] reported on a successful general physician-delivered penicillin allergy de-labeling program in hospitalized patients in the Netherlands. The intervention included physician education, distributing pocket-sized reminder cards, and electronic medical records to prompt physicians to perform the necessary assessment. Maguire *et al.*[29] reported a successful US emergency department physician-delivered, penicillin allergy de-labeling patient pathway. The intervention included the development of a penicillin and cephalosporin test dose procedure guideline, pharmacist-led education, physician-ordered test doses, pharmacist

verification, and nurse administration and post-challenge dose observation.

In this review, we aim to systematically examine the literature to identify and determine the effectiveness of interventions that enable non-allergy specialist health care workers to assess and, where appropriate, de-label adult and pediatric patients with a reported penicillin allergy in any health care setting. The review will also identify and synthesize those components of the interventions that make them safe and effective. A non-allergy specialist is defined as a medical professional whose primary specialization is not in allergy or who has not trained in allergy as part of their specialty.[30]

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted and no current systematic reviews on the topic were identified. However, one systematic review by Cooper *et al.*[17] was underway, synthesizing the evidence on the safety and efficacy of de-labeling penicillin allergy in adults using direct oral challenge. This has since been published, and shows that direct oral challenge delivered by both allergists and non-allergists, is safe and effective as a method of de-labeling adults. Our proposed systematic review will be more focused than that of Cooper *et al.*[17] because it will look solely at non-allergists. However, the scope will also be broader because the review will not be limited by health care setting. It will also consider children and adolescents as well as adults, and will include all methods to de-label patients with incorrect penicillin allergy labels. We will narrow our search to non-allergists because we wish to understand the wider frameworks that enable non-allergists to assess penicillin allergy records and safely de-label patients. If this issue is to be tackled at scale, we need to mobilize the non-allergist workforce and teach it how to do this safely.

The findings of this review will inform the development of a complex intervention designed to facilitate and embed penicillin allergy assessment and de-labeling. The intervention will be delivered by non-allergy specialists as part of a secondary care antimicrobial stewardship program in a UK hospital.

The objectives of this systematic review are to i) identify and synthesize the range of interventions and allergy testing methods used by non-allergists to assess reported penicillin allergies and subsequent de-labeling; ii) identify which types of health care workers have been targeted by interventions to assess and de-label penicillin allergy records (as per the first objective); and iii) determine the effectiveness (increased penicillin antibiotic use) and safety (absence of adverse drug events) of strategies used to deliver non-allergy specialist inpatient de-labeling in hospitalized patients.

Review question

What is the effectiveness and safety of interventions that facilitate non-allergy specialist health care workers' assessment of adults and pediatric patients with reported penicillin allergy, with subsequent de-labeling of erroneous records?

Inclusion criteria

Participants

This review will include studies with any patient (adults, adolescents, or children) who have a penicillin allergy record or self-reported allergy to penicillin, upon direct questioning, in any health care context and from any country.

Interventions

The review will include studies reporting on penicillin allergy de-labeling using any method (direct de-label, direct oral challenge, skin testing, or oral challenge) by non-allergy specialists, which include, but are not limited to, nurses, pharmacists, and physicians. Penicillin allergy assessment and de-labeling interventions delivered by immunologists or allergy specialists will be excluded.

Comparators

The comparators will be adults, adolescents, and children who receive usual standard care and do not undergo penicillin allergy assessment. Due to the nature of the intervention, there may not be a comparator group; therefore, studies without a comparator or control group will not be excluded.

Outcomes

The primary outcomes will be the number of adults, adolescents, or children with a penicillin allergy record who are successfully de-labeled. The secondary outcomes will be i) any measured antimicrobial stewardship impact (eg, antibiotic class prescribed, antibiotic cost, antibiotic side effects, treatment failure, health care associated infections, antibiotic resistant infections); ii) any measured health care

system impact (eg, length of hospital stay, health care resource utilization); and iii) any unintended harm associated with the de-labeling process (eg, anaphylaxis, side effects of antibiotics).

Types of studies

This review will consider both experimental and quasi-experimental study designs, including randomized controlled trials, non-randomized controlled trials, before and after studies, and interrupted time-series studies. In addition, the review will consider analytical observational studies, including prospective and retrospective cohort studies, case-control studies, analytical cross-sectional studies, and descriptive observational study designs. Case reports will be excluded.

Methods

The systematic review will be conducted in accordance with the JBI methodology for systematic reviews of effectiveness,[31] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[32]

The protocol has been registered in PROSPERO (CRD42020219044).

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of Embase was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for Embase (Ovid; Appendix I). The search strategy, including all identified keywords and index terms, will be adapted for each included database and/or information source. Backwards and forwards reference searches of all included sources of evidence will be completed to identify additional studies.

Only studies published in English will be included due to a lack of funding for translation services. No date limit will be set for included studies because this is a relatively new antimicrobial stewardship intervention, and studies are only expected to be identified from 2010 onwards.

The databases to be searched from their inception to the present day will include Embase (Ovid), MEDLINE (Ovid), CINAHL (Ovid), PsycINFO, Web of Science, and Cochrane CENTRAL. Sources of unpublished studies/gray literature will include the World Health Organization Library database, key organization websites and conference proceedings (eg, European Society of Clinical Microbiology and Infectious Diseases, Society for Healthcare Epidemiology of America, Healthcare Infection Society, Infection Prevention Society), registered controlled trial registers, technical or research reports from government agencies, and the British Library (EThOS) Collection of PhD dissertations.

We will contact known experts in the topic regarding any unpublished work and to ensure we have not overlooked relevant literature.

Study selection

Following the search, all identified citations will be collated and uploaded into Endnote Note v.X9.2 (Clarivate Analytics, PA, USA) and duplicates removed. Following a pilot test, titles and abstracts will then be screened by at least two independent reviewers for assessment against the inclusion criteria for the review using RAYYAN software (Qatar Computing Research Institute, Doha, Qatar). Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).[33] The full text of selected citations will be assessed in detail against the inclusion criteria by at least two independent reviewers using RAYYAN software. Reasons for exclusion of papers at full text that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer. The results of the search and the study inclusion process will be reported in full and presented in a PRISMA flow diagram.[32]

Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality using standardized critical appraisal instruments from JBI for experimental, quasi-experimental, observational, and descriptive studies.[31] Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion or with a third reviewer.

The results of the critical appraisal will be reported in narrative format and in a table.

Studies will not be excluded on the grounds of their risk of bias, but the risk of bias will be reported when presenting the results. The risk of bias judgments will be summarized across different studies for each of the domains listed using the risk of bias graph and the risk of bias summary. Therefore, all studies, regardless of the results of their methodological quality, will undergo data extraction and meta-analysis, where possible.[31]

Data extraction

Data will be extracted from studies included in the review by two independent reviewers using the standardized data extraction tool from JBI.[31] The extracted data will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objectives and interventions. These data will be categorized using Cochrane's Effective Practice and Organisation of Care taxonomy of health interventions.[34] Authors of papers will be contacted to request missing or additional data, where required.

Data synthesis

Studies will, where possible, be pooled in statistical meta-analysis using JBI SUMARI.[33] Effect sizes will be expressed as either odds ratios (for dichotomous data) or weighted (or standardized) final post-intervention mean differences (for continuous data), and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard χ^2 and I^2 tests, and reasons for heterogeneity will be explored using subgroup and/or sensitivity analyses. Subgroups may include the penicillin allergy de-label method used (eg, direct de-label, direct oral challenge), the setting (inpatient or outpatient), or patient age (adults, adolescents, or children). Statistical analyses will be performed using the random effects model, or if study numbers are small, the fixed effects model.[35] Where statistical pooling is not possible, the findings will be presented in narrative format, including tables and figures, to aid in data presentation. A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test)[36-38] will be performed where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed,[39] and a Summary of Findings (SoF) will be created using GRADEpro GDT 2020 (McMaster University, ON, Canada). The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. The outcomes reported in the SoF will be the proportion of adults, adolescents, or children with a penicillin allergy record who have been successfully de-labeled; any measured antimicrobial stewardship impact; any measured health care system impact; and any unintended harm associated with the de-labeling process.

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Appendix I: Search strategy

Embase (Ovid) searched October 16, 2020

1. (penicillin adj2 allerg*).tw.
2. (penicillin adj2 hypersensitiv*).tw.
3. (penicillin adj2 anaphylaxis).tw.
4. (beta-lactam adj2 allerg*).tw.
5. (beta-lactam adj2 hypersensitiv*).tw.
6. (beta-lactam adj2 anaphylaxis).tw.
7. (''betalactam'' adj2 anaphylaxis).tw.
8. (''betalactam'' adj2 hypersensitiv*).tw.
9. (''betalactam'' adj2 allerg*).tw.
10. (''*lactam'' adj2 allerg*).tw.
11. (''*lactam'' adj2 hypersensitiv*).tw.
12. (''*lactam'' adj2 anaphylaxis).tw.
13. (''antibiotic'' adj2 anaphylaxis).tw.
14. (''antibiotic'' adj2 hypersensitiv*).tw.
15. (''antibiotic'' adj2 allerg*).tw.
16. (''antimicrobial'' adj2 allerg*).tw.
17. (''antimicrobial'' adj2 hypersensitiv*).tw.
18. (''antimicrobial'' adj2 anaphylaxis).tw.
19. ''PENICILLIN DERIVATIVE''/
20. ''DRUG HYPERSENSITIVITY''/ or ANAPHYLAXIS/
21. 19 and 20
22. ''PENICILLIN ALLERGY''/
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18or 21 or 22
24. ''clinical decision tool''.tw.
25. ''clinical decision making''.tw.
26. ''clinical assessment tool''.tw.
27. direct.tw.
28. challenge.tw.
29. de-label*.tw.
30. 27 and 28
31. delabel*.tw.
32. ''interview''.tw.
33. ''antibiotic stewardship''.tw.
34. ''antimicrobial stewardship''.tw.
35. test*.tw.
36. ''allergy assess*''.tw.
37. ''oral challeng*''.tw.
38. ''ANTIMICROBIAL STEWARDSHIP''/
39. ''SKIN TEST''/
40. ''PROVOCATION TEST''/

41. "ALLERGY TEST"/
42. "CLINICAL EVALUATION"/
43. ALGORITHM/
44. "RISK ASSESSMENT"/
45. 24 or 25 or 26 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 23 and 45

No limits set, number of returns 3188.